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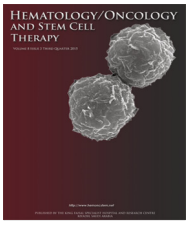

LETTER TO EDITOR

Impact of conditioning and engraftment on iron status in hematopoietic stem cell transplantation: Contribution of labile plasma iron

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Nontransferrin-bound iron has been reported shortly after myeloablative conditioning in patients undergoing hematopoietic stem cell transplantation (HSCT). It is assumed that the appearance of unbound iron in this setting possibly reflects a major disturbance in body iron distribution, which is related mainly to its underutilization due to erythropoiesis suppression [1,2]. Other alternative explanations for the release of unbound iron in this setting include chemotherapy-induced apoptosis of a large number of erythroid progenitors, and release and degradation of a large amount of hemoglobin from them. There is a concern that labile plasma iron (LPI), the most toxic fraction of nontransferrin-bound iron that includes the redox-active forms of iron, may be involved in the occurrence of toxicity and other complications commonly observed in the early post-HSCT period [3,4].

Recently, we demonstrated that LPI levels, albeit normal at baseline measurements, increased substantially 48 hours after the start of conditioning in HSCT patients, with a peak around Day 0, and remained increased until engraftment, when it returned to normal levels [5]. Here, we provide a more comprehensive analysis of iron status in HSCT patients by adding determinations of hepcidin and standard iron parameters along with LPI levels in 25 adult patients undergoing first autologous HSCT following myeloablative conditioning. This study was approved by the local Institutional Review Board and was conducted in compliance with the Declaration of Helsinki.

All iron parameters were determined before the start of conditioning (baseline), on Day 0 (before stem cell infusion), and on documented engraftment in 25 auto-HSCT adult patients. Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of at least 0.5×10^9/L. LPI and standard iron parameters were determined as previously described [5,6]. Hepcidin was determined by the DRG Hepcidin-25 (bioactive) enzyme-linked immunosorbent assay (DRG International, Inc., USA).

The characteristics of the study population are summarized in Table 1. All 25 patients engrafted (mean 12 days, range 9–16 days) and received red blood

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Table 1 Patient characteristics (n = 25).

Mean age (y), range	46 (21—68)
Sex (M/F)	10/15
Underlying disease	
Multiple myeloma	13
Malignant lymphoma	8
Acute leukemia	3
Seminoma	1
Disease status	
Complete remission	12
Partial remission	10
Relapse, refractory	3
Previous RBC transfusions	
None	12
<10 units	9
>20 units	4
Type of conditioning	
Mel200	11
CVB	7
BuMel	3
Others[a]	4

Note. BuMel = busulfan + melphalan; CVB = cyclophosphamide + BCNU + etoposide; Mel200 = melphalan 200 mg/m^2; RBC = red blood cell.

[a] BCNU (carmustine) + etoposide + cytarabine + melphalan (n = 2), carmustine + etoposide + cyclophosphamide (n = 1), and busulfan + cyclophosphamide + etoposide (n = 1).

cell transfusion during their admission (only from Day 0 until engraftment, mean 3 units, range 1—7 units).

The fast and substantial increase in LPI levels on Day 0 indeed reflected a disruption of iron homeostasis by conditioning, which was accompanied by a response in hepcidin and transferrin saturation (TfS) levels (Table 2). In addition, it can be speculated that the conditioning-induced ablation of erythropoiesis could reduce the synthesis of erythroferrone, an erythroid hormone that suppresses hepcidin, favoring increased hepcidin levels [7]. During the aplasia phase, only four patients presented fever due to infectious complications, but their iron parameters were within the average range reported in Table 2.

However, reutilization of iron by restored erythropoiesis on engraftment leads to a substantial drop in LPI levels, but not in hepcidin levels, possibly due to the fact that production of hepcidin by the liver is modulated not only by iron loading and erythropoietic activity, but also by inflammation. Among several inflammatory stimuli reported to induce hepcidin expression, the mechanism involving interleukin-6 has been defined most clearly [8]. In fact, parallel elevations of interleukin-6 and hepcidin levels at 1 week after HSCT were already reported, strengthening the hypothesized role of the inflammatory pathway, rather than iron signals, in hepcidin synthesis until occurrence of engraftment [9].

Baseline ferritin levels were already increased and did not change throughout the study. This pattern was previously reported in HSCT patients, where baseline serum ferritin levels were increased in a similar manner to the levels presented in this study and also changed very little within the first 2 weeks following HSCT [9]. The fact that many patients underwent mobilization with chemotherapy, usually within 1 month prior to the start of conditioning, may have contributed to increased baseline ferritin levels. As ferritin levels take longer to return to normal compared with hepcidin after a chemotherapy-associated inflammatory episode, baseline levels could be expected to differ between these two parameters in this study.

Considering all determinations (at baseline, on Day 0, and on engraftment), hepcidin levels correlated positively with ferritin (Fig. 1A) and TfS (Fig. 1B), and LPI levels correlated positively with ferritin (Fig. 1C) and TfS (Fig. 1D). Interestingly, increased LPI levels were observed with normal TfS levels in some patients. A tendency of a correlation between hepcidin and LPI was found considering only baseline and Day 0 levels (Fig. 1E), but was lost when engraftment levels were included, possibly due to the reasons mentioned above.

As expected, one can be concerned about the applicability of these results to clinical practice. Previously, we reported that baseline LPI levels could predict the occurrence of Grade III or IV toxicity in HSCT patients, provided that this should be confirmed in a larger and more homogeneous group of patients [5]. Once the relationship between increased LPI levels and early toxicity is confirmed, chelation may have a role in HSCT patients. Moreover, if chelation is to be used early in HSCT, administration of deferasirox for 5 days, starting on the 1st day of conditioning, was shown to be very effective in preventing increments in LPI levels in HSCT patients [10].

Our updated results showed that cytotoxic chemotherapy and subsequent engraftment in HSCT patients lead to changes in all iron parameters (LPI, hepcidin, and TfS), except for ferritin. The results indicate that, among these iron parameters, LPI reflected better the modifications in

Table 2 Iron parameters in 25 HSCT patients.

	Baseline	Day 0	Engraftment
LPI (μM)[a]	0.3 ± 0.06	3.1 ± 0.6*	0.4 ± 0.2
Hepcidin (ng/mL)	25.1 ± 3.9	40.0 ± 3.5*	39.1 ± 3.3*
Transferrin saturation (%)	40.0 ± 2.8	70.0 ± 3.8*	47.9 ± 5.9
Ferritin (ng/mL)	733 ± 55	782 ± 47	778 ± 33

Note. Values represent mean ± SEM. HSCT = hematopoietic stem cell transplantation; LPI = labile plasma iron; SEM = standard error of the mean.

[a] LPI levels of <0.5 μM are considered normal.

* p < .05 in relation to baseline levels.

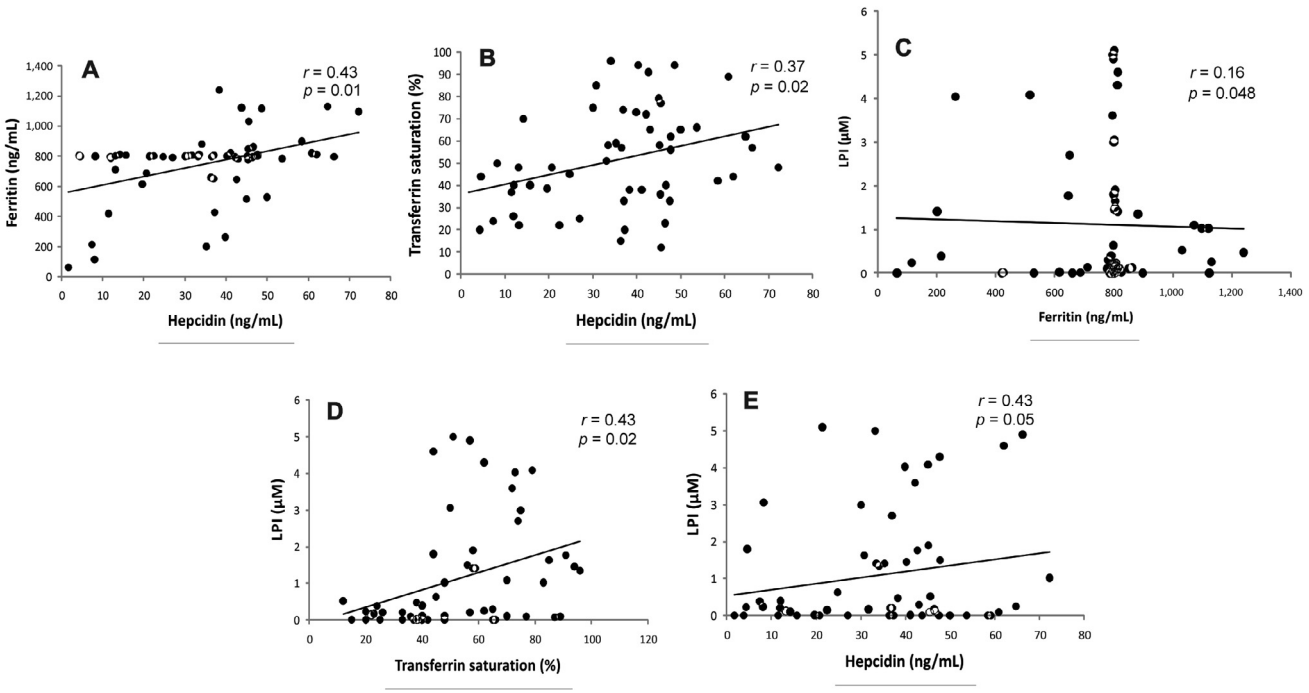

Fig. 1 Correlations between ferritin and hepcidin (A), transferrin saturation and hepcidin (B), LPI and ferritin (C), LPI and transferrin saturation (D), and LPI and hepcidin (E) levels throughout the study. *Note*. LPI = labile plasma iron.

iron status caused by conditioning and could serve as a target in the eventuality of chelation therapy in the early period of HSCT. The other iron parameters, including hepcidin, were probably influenced by inflammation, even on engraftment, and would not behave as appropriate surrogate markers for increased LPI levels.

Conflicts of interest

All authors declare no potential conflicts of interest.

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